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Full-length Article

Perceived stress and telomere length: A systematic review, meta-analysis, and methodologic considerations for advancing the field

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ABSTRACT

Importance: Psychological stress contributes to numerous diseases and may do so in part through damage to telomeres, protective non-coding segments on the ends of chromosomes.
Objective: We conducted a systematic review and meta-analysis to determine the association between self-reported, perceived psychological stress (PS) and telomere length (TL).
Data sources: We searched 3 databases (PubMed, PsycInfo, and Scopus), completed manual searches of published and unpublished studies, and contacted all study authors to obtain potentially relevant data.
Study selection: Two independent reviewers assessed studies for original research measuring (but not necessarily reporting the correlation between) PS and TL in human subjects. 23 studies met inclusion criteria; 22 (totaling 8948 subjects) could be meta-analyzed.
Data extraction and synthesis: We assessed study quality using modified MINORS criteria. Since not all included studies reported PS–TL correlations, we obtained them via direct calculation from author-provided data (7 studies), contact with authors (14 studies), or extraction from the published article (1 study).
Main outcomes and measures: We conducted random-effects meta-analysis on our primary outcome, the age-adjusted PS–TL correlation. We investigated potential confounders and moderators (sex, life stress exposure, and PS measure validation) via post hoc subset analyses and meta-regression.
Results: Increased PS was associated with a very small decrease in TL ($n = 8724$ total; $r = -0.06$; 95% CI: $-0.10, -0.008$; $p = 0.01$; $\alpha = 0.025$), adjusting for age. This relationship was similar between sexes and within studies using validated measures of PS, and marginally (nonsignificantly) stronger among samples recruited for stress exposure ($r = -0.13$; vs. general samples: $b = -0.11$; 95% CI: $-0.27, 0.01$; $p = 0.05$; $\alpha = 0.013$). Publication bias may exist; correcting for its effects attenuated the relationship.
Conclusions and relevance: Our analysis finds a very small, statistically significant relationship between increased PS (as measured over the past month) and decreased TL that may reflect publication bias, although fully parsing the effects of publication bias from other sample-size correlates is challenging, as discussed. The association may be stronger with known major stressors and is similar in magnitude to that noted between obesity and TL. All included studies used single measures of short-term stress; the literature suggests long-term chronic stress may have a larger cumulative effect. Future research should assess for potential confounders and use longitudinal, multidimensional models of stress.

1. Introduction

Unmanaged psychological stress is pervasive in many modern societies. American adults consistently report moderately high levels of stress, with 53% believing they have experienced personal health problems as a result of stress and only 29% reporting that they are doing a "very good" or "excellent" job of managing or reducing stress (Anderson et al., 2012). Self-reported stress has increased in nearly every demographic between 1983 and 2009 (Cohen and Janicki-Deverts, 2012).

High levels of chronic stress are associated with numerous diseases and deleterious conditions, including obesity and abdominal

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fat deposition (Dallman et al., 2003), metabolic syndrome (Chandola et al., 2006), respiratory infection (Cohen et al., 1991), immune compromise (Kiecolt-Glaser et al., 1996; Antoni et al., 2006), cardiovascular disease (Iso et al., 2002), systemic inflammation (Everson-Rose and Lewis, 2005; Miller and Blackwell, 2006; Yudkin et al., 2000), respiratory impairment (Lehrer, 2006), tumor growth (Antoni et al., 2006), and dendritic shortening in the hippocampus and prefrontal cortex (McEwen, 2008). Mouse models have demonstrated that catecholamine stimulation (simulating the hormonal effects of chronic stress) causes systemic damage to chromosomes (Hara et al., 2011).

Telomeres are non-coding, repetitive nucleotide segments on the ends of each mammalian chromosome that serve a protective role during DNA transcription. A small number of base pairs at the ends of a chromosome are lost during each transcription, resulting in an overall shortening of the chromosome after many duplications. Telomeres therefore serve as a protective "buffer" to prevent the truncation of functional coding segments during duplication. Although telomeres are routinely replenished by telomerase, their gradual attrition over the lifespan may contribute to disease. Recent studies have explored the relationship between telomere length and health (Epel et al., 2004) and found short telomeres to be a risk factor for many diseases of aging, including cancer (Wentzensen et al., 2011), cardio-metabolic dysfunction (D'Mello et al., 2015), and diabetes (Zhao et al., 2013).

Stressed, depressed, anxious, or previously traumatized individuals may have shorter telomeres than their psychologically healthy counterparts (Epel et al., 2004, 2006; Okereke et al., 2012; Tyrka et al., 2010; Simon et al., 2006; O'Donovan et al., 2011). For example, recent stressor exposure within the last five years (but not earlier) (Verhoeven et al., 2015) as well as chronic social stress (Oliveira et al., 2015) are associated with shorter telomeres. Since the first study documenting a relationship between telomere length and perceived stress (Epel et al., 2004), many studies measuring telomere length have included a measure of psychological stress; however, relatively few have reported the effects of perceived stress on telomere length.

Stress is not a unitary construct, but rather comprises exposure to stressors, perception of stress, and the physiological stress response. Exposure to chronic stressors (such as domestic abuse) may provoke sustained physiological stress arousal, which in turn could impact telomere biology (Fig. 1). Indeed, experimental research in animal models and epidemiological research in humans suggests that central elements of the physiological stress response (namely cortisol exposure and individual cortisol reactivity) are associated with shortened telomeres (Haussmann and Heidinger, 2015; Gotlib et al., 2015; Tomiyama et al., 2012). The presence of a chronic stressor potentially indicates that an individual's current perceived stress is reflective of a chronic, rather than short-lived, psychological state. Thus, the conceptual model in Fig. 1 predicts that perceived stress may be more strongly related to telomere length in the presence of a chronic stressor, a possibility addressed in the present analysis.

A previous meta-analysis including only a small number of studies that explicitly reported correlations between perceived stress and telomere length detected publication bias and called for additional research (Schutte and Malouff, 2014). Additional methodological limitations motivate the present analysis. For example, 2 studies in the previous analysis shared subjects (Epel et al., 2004; Tomiyama et al., 2012), resulting in double-counting. Finally, statistically distinct effect sizes (for example, correlations adjusting for different sets of covariates) were synthesized, resulting in pooled point estimates with limited interpretability. We aimed to build on these preliminary results by conducting a more exhaustive review of the existing literature, addressing the methodological challenges of the prior analysis.

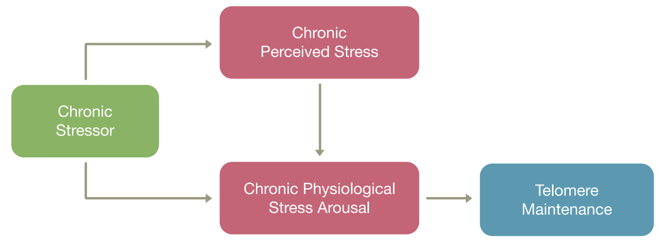

Fig. 1. The stress triad and telomere maintenance. Chronic major stressor exposures can lead to chronically high levels of perceived stress and subsequent stress arousal. In turn, chronic stress arousal is hypothesized to proximally impact telomere maintenance. To the extent that perceived stress over the month reflects a chronic state and is related to stress arousal, there may be a relationship between perception and telomere length.

An additional, novel objective was to assess demographic and methodological factors that may confound or moderate the PS–TL relationship. First, psychometric validity and reliability vary across measures of PS; for example, conceptually distinct but associated constructs such as negative affect and trait neuroticism may contaminate PS measurement (Cohen and Williamson, 1988). Second, because females tend to have longer telomeres (Gardner et al., 2014), but higher PS (Cohen and Janicki-Deverts, 2012), than males, sex could act as a suppressor or moderator variable. Third, the PS–TL relationship may differ substantially for subjects with a known major stressor or a physical health condition, both of which may be associated with PS and TL (Holmes and Rahe, 1967; Dohrenwend and Dohrenwend, 1982; Turner et al., 1995). We quantitatively investigated these possible effects using meta-regressive methods and subset analyses.

In order to include both the growing published literature on perceived stress and telomere length as well as data not previously synthesized meta-analytically, we performed a systematic review using a comprehensive search strategy and inclusion criteria directed at capturing unreported correlations, unpublished data, and recent additions to the literature. We quantitatively meta-analyzed the association of perceived stress with telomere length.

2. Methods

2.1. Data sources and searches

We systematically searched PubMed, PsycInfo, and Scopus from inception to April 2015 to identify all studies published in any language collecting any measure of telomere length (TL) and self-reported, perceived psychological stress (PS) in human subjects. We developed search strategies[1] in consultation with a professional reference librarian; the search strings captured PS via terms including *stress*, *dysthymia*, *anxiety*, and *trauma* and captured TL via terms including *telomere*, *oxidative stress*, and *cell aging*. Search terms were deliberately broad in order to capture all potentially relevant articles; a later review process (detailed below) excluded the numerous articles failing to meet specific inclusion criteria.

[1] Specific search strings were as follows. *PubMed:* (dysthym* [ti] OR pessim* [ti] OR "anxiety" [mesh] OR "anxiety" [tiab] OR "bipolar disorder" [mesh] OR "bipolar disorder" [tiab] OR depress* [ti] OR adversity* [ti] OR traum* [ti] OR stress* [ti] OR "stress, psychological" [mesh] OR "mood disorders" [mesh] OR "mental disorders" [mesh] OR "psychology" [sh] OR cognit* [ti]) AND (telomere* [ti] OR "telomere" [mesh] OR "chromosome breakage" [mesh] OR "matched pair analysis" [mesh] OR "cell aging" [mesh]) NOT (oxidative [ti] OR "oxidative stress" [mesh] OR editorial [pt] OR letter [pt] OR "review" [pt]) NOT ("animals" [mesh] NOT "humans" [mesh]). *PsycInfo:* (telomer*.mp. or telomere length.id. or telomere biology.id.) and (exp stress/ or stress*.mp. or exp mental health/) *Scopus:* KEY(telomer*) AND KEY(chronic stress OR mental stress).

We reviewed included articles' references for potentially relevant articles that had not been captured in the database search and conducted manual searches for published and unpublished studies in consultation with an experienced researcher in the field (EE). We conducted the final search on April 3, 2015.

2.2. Study selection

Among the articles of any design and written in any language retrieved from the initial, broad database search, we included in analysis studies that: (1) represented original research (excluding systematic reviews, narratives, meta-analyses, etc.); (2) used human subjects (excluding animal and in vitro studies); (3) measured both TL and self-reported PS for at least a subset of subjects. We included studies measuring PS only as a covariate, even when the association between PS and TL was not reported.

2.3. Data extraction and quality assessment

We performed article screening using web-based systematic review software DistillerSR (Evidence Partners, Ottawa, Canada). Two investigators (MM and SK) independently assessed each article against the inclusion criteria, resolving disagreements through re-review, discussion, and arbitration by a referee (NK). Both investigators first assessed only titles and abstracts in order to exclude articles lacking a measure of TL. For the remaining articles, the investigators then obtained full texts as necessary to assess the remainder of the inclusion criteria. We assessed methodological quality of eligible studies using modified MINORS criteria (Slim et al., 2003), assessing clarity of aims and inclusion criteria, description of a priori data collection and analysis plans, prospective calculation of sample sizes, quality of the PS and TL variables, blinded assessment of TL, and reporting of missing data.

2.4. Data collection

Two investigators (MM and EE) contacted authors for each eligible study to request summary statistics or preferably raw data, including measures of TL, PS, age, and sex. For the studies for which we obtained raw data, MM re-analyzed the raw data to confirm published statistics related to the PS–TL relationship, resolving any discrepancies through discussion with the authors. Summary measures included the raw correlation between PS and TL, the partial correlation adjusting for age (henceforth "age-adjusted"), and the age- and sex-adjusted correlation, as well as the age-adjusted, sex-stratified correlation. When no endpoints of interest nor mathematically equivalent statistics were available, we searched for other relevant statistics on the relationship between PS and TL (such as rank correlations) for qualitative description. Finally, for eligible studies sharing an author, we verified with authors whether there was any duplication of subjects between studies and used this information to eliminate duplicated data.

2.5. Protocol modifications

We clarified the inclusion criteria post hoc in the following instances: (1) 3 studies measured domain-specific stress (stress specifically related to the duties of a schoolteacher (von Känel et al., 2015), stress in 8 domains [such as career- and relationships-related] (Litzelman et al., 2014), and instantaneous state stress immediately before exposure to a laboratory stressor (Zalli et al., 2014). Because a priori inclusion criteria did not adequately address eligibility of such measures, we excluded these studies, further refining the inclusion criterion to include only studies measuring global perceived stress; (2) 1 study (Kananen et al., 2010) employed the Global Health Questionnaire (GHQ-12) measure. Upon reviewing and excluding a later article that included a more detailed description of the GHQ-12 measure, reviewers agreed that this measure did not meet inclusion criteria, and this study was excluded; (3) 1 article identified via manual search (Hoen et al., 2011) made no mention of PS, but was included because author EE was aware the study had collected PS measures based on other publications from the study.

2.6. A priori endpoints

The primary outcome and predictor variables of interest were TL and PS; the primary analytic goal was to synthesize data on their relationship. Because TL declines with age (Benetos et al., 2001; Brouilette et al., 2007), we assessed age as a covariate and likely confounder by additionally estimating the age-adjusted partial correlation between PS and TL through meta-analytic methods. Thus, we specified 2 endpoints a priori: (1) the age-adjusted Pearson correlation between PS and TL (primary); and (2) the raw, unadjusted Pearson correlation between PS and TL (secondary).

2.7. Moderator and subgroup analyses

As described in the Introduction, demographic variables such as sex and past exposure to a major stressor, as well as methodological factors such as psychometric quality of PS measures, may confound or moderate the PS–TL relationship. Based on these hypothesized effects, we investigated 4 post hoc endpoints and subset analyses: (1) we examined the age-adjusted PS–TL correlation among only studies employing an empirically validated measure of PS. All subsequent secondary analyses were also conducted among only this subset of studies; (2) we examined the age- and sex-adjusted PS–TL correlation and the moderation effect of sex; (3) we investigated possible effects of sample heterogeneity by characterizing the PS–TL relationship according to the type of sample enrolled using 3 mutually exclusive categories: "General samples" included those not specifically selected for physical health conditions or stress exposures (these samples mostly comprised healthy adults, but subjects with physical health conditions or stress exposures were not excluded); "stress-exposed samples" included those selected for exposure (past or present) to a major stressor such as traumatic events or caregiving responsibilities for those with medical illness (this category included studies enrolling both stressed and control subjects); "physical condition samples" included those selected for the presence of a disease or other physical condition.

Many such studies involved diseases known to be comorbid with stress or depression. In addition, in the samples that did not recruit specifically for a disease group, we coded whether there were exclusion criteria to rule out major diseases such as cardiovascular disease, diabetes, or cancer. Because specific physical conditions may have strong effects on telomere biology, these samples were not included in the stress-exposed category (which in most cases were healthy samples where major diseases were excluded; Table 1).

2.8. Comparative analysis for limitations of PS measures

A gold standard predictor variable for stress would accurately measure physiological stress as the most proximal stress-related influence on telomere degradation. Discrepancies between perceived, physiological, and reported stress could mask a stronger effect of proximal physiological factors on telomere shortening. We planned to conduct an exploratory analysis comparing the magnitudes of PS–TL relationships to physiological stress-TL relationships among studies collecting both measures of stress. We reviewed Google Scholar and PubMed using combinations of the search terms *psychological stress*, *perceived stress*, *physiological stress*, and *cortisol*.

2.9. Statistical analysis

We conducted all statistical analyses in R (Version 3.1.0, multiple contributors, Vienna, Austria)[2]. We adjusted analyses for multiple comparisons via the Šidák method, applying a standard family-wise error rate of $\alpha = 0.05$ to the 2 primary analyses and to the 4 post hoc analyses separately. This yielded an adjusted $\alpha = 0.025$ for each primary analysis and $\alpha = 0.013$ for each post hoc analysis. We adjusted all confidence intervals accordingly; *p*-values are unadjusted and reported with corresponding adjusted α levels. We did not apply multiplicity adjustments to sensitivity analyses.

We preferentially computed effect size measures from raw data; for studies without available raw data, we used summary correlations provided by authors or published effect size measures. Common measures of PS are many-item composite scores that can reasonably be treated as continuous. 1 study (Surtees et al., 2011) with available raw data included a covariate corresponding to assay plate; we additionally adjusted for this variable in all correlation measures for this study. We used Fisher's *r*-to-*z* transformation for variance stabilization and normalization (Borenstein and Hedges, 2009) and reconverted all reported results to *r* scale. We pooled point estimates via linear mixed-effects modeling (allowing random effects by study) estimated via restricted or unrestricted maximum likelihood estimation. Models employed inverse-variance weighting, and we based inference on pooled estimates on the *t*-distribution using Knapp–Hartung adjusted standard errors (an adjustment to the DerSimonian–Laird method with improved statistical properties) (IntHout et al., 2014).

We estimated and tested for between-study effect heterogeneity using (1) Cochran's *Q*, a weighted sum of squares on a standardized scale and the associated chi-square statistic, and (2) *T*, the estimated standard deviation of true effects across studies (Borenstein and Hedges, 2009). Finally, using the available raw data, we visually examined scatterplots to evaluate model assumptions – for example, by assessing the linearity of the relationship between PS and TL and the possible presence of systematically occurring influential outliers.

We used the same modeling approach in post hoc analyses as in main analyses but excluded studies using an unvalidated stress measure. We made the distinction between validated and unvalidated measures post hoc. Therefore, in keeping with our a priori analysis plan, we included both types of measures in primary analyses to avoid inflation of α levels due to post hoc changes to analyses (Simmons et al., 2011). For secondary analyses, we also report results of sensitivity analyses in which no studies were excluded, as in primary analyses.

We estimated the pooled, age-adjusted PS–TL correlation among this subset of studies. We further investigated the effect of sex as a confounder by estimating the age- and sex-adjusted pooled correlation. To investigate whether sex might moderate the PS–TL relationship, we stratified study samples by sex and used meta-regression (introducing a fixed covariate effect to the random-effects model); this coefficient represents the estimated difference in PS–TL correlation for females versus males. We used a similar approach to assess whether sample type (general population, samples selected for a physical condition, or samples selected for stress exposure) moderated the PS–TL relationship; the corresponding coefficients represent the difference in point estimates across the 3 types of samples. For each meta-regressive model as well as for a comparable "reduced" model not containing the moderator of interest, we computed Higgins' residual I^2 statistic, which estimates the proportion of residual variance attributable to true inter-study heterogeneity in effect sizes (Borenstein and Hedges, 2009). A much smaller residual I^2 in the full model, compared to the reduced model, would suggest that the moderator variable of interest may have contributed strongly to inter-study effect heterogeneity.

2.10. Sensitivity analyses for publication bias

We used a funnel plot and Egger's test (Borenstein and Hedges, 2009), a meta-regressive estimate of the association of a study's point estimate with its standard error (SE), to assess for possible publication bias or other systematic effects of sample variability. If the PS–TL relationship is truly stronger for samples recruited for a physical condition or major stressor (which are likely to be smaller in size and higher in SE) than for the general population, such an effect could spuriously produce the appearance of publication bias. Therefore, we also conducted a modified Egger's regression containing fixed-effects of both study SE and sample type. We then used the likelihood-ratio chi-square test to assess whether removing the coefficient for study SE significantly worsened model fit; a significant result would suggest that any tendency of smaller studies to report larger correlations cannot be attributed to differences in sample demographics alone, and would more strongly indicate publication bias. Finally, we used the Duval approach (Duval and Tweedie, 2000) to estimate a trimmed-and-filled, age-adjusted point estimate. We planned to conduct an exploratory analysis comparing physiological to perceived stress measures, but limitations of the published literature made this unfeasible.

3. Results

3.1. Study eligibility and data collection

Our literature search retrieved 2,192 potentially relevant articles across all 4 databases (Fig. A.1). We removed 115 duplicated articles. Of the remaining 2077 unique articles, we excluded 1620 articles that clearly did not measure TL after abstract and title screening. We found an additional 3 potentially relevant articles (Hoen et al., 2011; Bersani et al., 2016; Friedman et al., 1988) via manual search. After abstract or full-text article review of the remaining 460 articles, we excluded 431 that failed to meet all inclusion criteria, leaving 29 relevant articles (Epel et al., 2004, 2006, 2012; Tyrka et al., 2010; Hoen et al., 2011; Surtees et al., 2011; Bersani et al., 2016; Uchino et al., 2012, 2015; Hassett et al., 2012; Sibille et al., 2012; O'Donovan et al., 2009, 2012; Puterman et al., 2010; Humphreys et al., 2012; Georgin-Lavialle et al., 2014; Wikgren et al., 2012; Entringer et al., 2011; Parks et al., 2009, 2011; Geronimus et al., 2010; Kiefer et al., 2008; Ludlow et al., 2008; Chen et al., 2015; Carlson et al., 2015; Tyrka et al., 2015; Buss et al., 2014; Prather et al., 2014) that met all inclusion criteria. Inter-rater agreement for study eligibility was 99.5% ($\kappa = 0.86$); we resolved 10 disagreements through discussion.

In correspondence with study authors, we identified instances of subject duplication in included studies and excluded an additional 6 articles (Epel et al., 2006; O'Donovan et al., 2009, 2012; Parks et al., 2009; Kiefer et al., 2008; Uchino et al., 2015). 1 included study (Parks et al., 2011) used a subset of data from the National Institute of Environmental Health Sciences (NIEHS) "Sister Study". We obtained data directly from NIEHS for all Sister Study subjects with data for PS and TL, resulting in a larger sample size in our analysis than was used in the corresponding paper. Data obtained from the NIEHS represented 2 heterogeneous sub-studies

[2] We used the following packages: *xlsx*, *reshape2*, *ggplot2*, *metafor*, *lme4*, *lmerTest*, *Amelia*, *car*.

Table 1
Characteristics of all eligible studies.

Study	Sample demographics[a]	Sexes enrolled	Sample classification	Major disease excluded	Main endpoint	Perceived stress measure	Data source	TL assay type	TL cell type	TL assay CV	Age-adjusted correlation
Bersani et al. (2016)	Male combat veterans, some with PTSD ($n = 76$)	Males	Stressed	No	Association of psychiatric measures with TL	Perceived Stress Scale (10-item)	Summary statistics from author	PCR	Blood (PBMC)	4.00%	−0.3
Buss et al. (2014)	Females, overweight or obese ($n = 42$)	Females	Physical condition	No	Associations of eating behaviors and metabolic profile with TL	Perceived Stress Scale (10-item)	Summary statistics from author	PCR	Blood (leukocyte)	4.00%	0.01
Carlson et al. (2015)	Female breast cancer survivors, distressed ($n = 87$)	Females	Physical condition	No	Effect of psychosocial interventions (randomized) on TL	Symptoms of Stress Scale (C-SOSI, 56-item)	Summary statistics from author	PCR	Blood (leukocyte)	Not calculated	−0.1
Chen et al. (2015)	Adults, caregivers of disabled children ($n = 89$)	Both	Stressed	No	Association of smoking and PS with TL	Perceived Stress Scale (14-item)	Summary statistics from author	PCR	Salivary	11.00%	−0.07
Entringer et al. (2011)	Adults, some whose mothers were psychologically stressed during pregnancy ($n = 98$)	Both	Stressed	Yes	Association of maternal stress status with offspring's TL	Perceived Stress Scale (10-item)	Summary statistics from author	PCR	Blood (leukocyte)	4.00%	−0.15
Epel et al. (2004)	Females, premenopausal mothers with chronically ill child and premenopausal normal mothers ($n = 57$)	Females	Stressed	Yes	Association of PS and caregiving status with TL	Perceived Stress Scale (10-item)	Summary statistics from author	PCR	Blood (PBMC)	Not calculated	−0.31
Epel et al. (2012)	Females, healthy with high education levels and low stress ($n = 258$)	Females	General	No	Association of mind-wandering with TL	Perceived Stress Scale (10-item)	Summary statistics from author	PCR	Blood (PBMC)	4.00%	−0.09
Georgin-Lavialle et al. (2014)	Adults, mastocytosis patients, 79% with some grade of depression ($n = 19$)	Both	Physical condition	No	Association of negative emotionality with TL	Perceived Stress Scale (14-item)	Data from author	PCR	Blood (PBMC)	Not calculated	−0.73
Geronimus et al. (2010)	Females, middle-aged, premenopausal, half Black ($n = 215$)	Females	General	No	Differences in TL between black and white subjects	Perceived Stress Scale (4-item)	Published article	PCR	Blood (PBMC)	4.50%	N/A
Hassett et al. (2012)	Females, fibromyalgia ($n = 61$)	Females	Physical condition	Yes	Association of pain with TL	Perceived Stress Scale (4-items)	Summary statistics from author	PCR	Blood (leukocyte)	3.00%	−0.21
Hoen et al. (2011)	Adults, stable coronary heart disease, many with major depression ($n = 949$)	Both	Physical condition	No	Association of depression with TL	Perceived Stress Scale (4-item)	Summary statistics from author	PCR	Blood (leukocyte)	3.70%	−0.06
Humphreys et al. (2012)	Females, formerly abused and non-abused ($n = 102$)	Females	Stressed	Yes	Association of abuse status with TL	Perceived Stress Scale (10-item)	Summary statistics from author	PCR	Blood (PBMC)	3.50%	−0.025
Ludlow et al. (2008)	Adults, middle- to older-aged ($n = 60$)	Both	General	No	Association of physical activity with TL	Perceived Stress Scale (10-item)	Data from author	PCR	Blood (PBMC)	5%	−0.03
NIEHS Sister Study 1[b]	Females, middle-aged, sisters have breast cancer ($n = 1{,}085$)	Females	General	No	Causes and sequelae of breast cancer	Perceived Stress Scale (4-item)	Data from author	PCR	Blood (leukocyte)	11.00%	0
NIEHS Sister Study 2[b]	Females, middle-aged, sisters have breast cancer ($n = 632$)	Females	General	No	Causes and sequelae of breast cancer	Perceived Stress Scale (4-item)	Data from author	PCR	Blood (leukocyte)	8.50%	−0.04
Prather et al. (2014)	Adults, obese ($n = 87$)	Both	Physical condition	Yes	Association of sleep quality with multiple TL measures	Perceived Stress Scale (10-item)	Summary statistics from author	PCR	Blood (PBMC)	4.00%	0.03
Puterman et al. (2010)	Females, post-menopausal, some dementia caregivers ($n = 58$)	Females	Stressed	Yes	Interaction of exercise with PS–TL relationship	Perceived Stress Scale (10-item)	Summary statistics from author	PCR	Blood (leukocyte)	4.00%	−0.26
Sibille et al. (2012)	Adults, chronic pain from knee osteoarthritis and controls ($n = 36$)	Both	Physical condition	No	Association of chronic pain and PS with TL	Perceived Stress Scale (10-item)	Summary statistics from author	PCR	Blood (PBMC)	7.50%	−0.13

Table 1 (*continued*)

Study	Sample demographics[a]	Sexes enrolled	Sample classification	Major disease excluded	Main endpoint	Perceived stress measure	Data source	TL assay type	TL cell type	TL assay CV	Age-adjusted correlation
Surtees et al. (2011)	Females, middle-aged, White, probability sample of Norfolk residents ($n = 4,353$)	Females	General	No	Association of PS and emotional health with TL	Single 5-point item: perceived stress over past 10 years	Data from author	PCR	Blood (lymphocyte)	Not calculated	−0.02
Tyrka et al. (2010)	Adults, some with severe childhood abuse and non-abused controls ($n = 31$)	Both	Stressed	Yes	Association of childhood abuse with TL	Perceived Stress Scale (14-item)	Data from author	PCR	Blood (leukocyte)	4.30%	0.17
Tyrka et al. (2015)	Adults, history of psychopathology and/or childhood adversity and controls ($n = 289$)	Both	Stressed	Yes	Association of psychopathology and childhood adversity with TL	Perceived Stress Scale (14-item)	Summary statistics from author	PCR	Blood (leukocyte)	4.54%	−0.1
Uchino et al. (2012)	Adults, middle- to older-age ($n = 136$)	Both	General	No	Association of social relationship type with TL	Perceived Stress Scale (10-item)	Data from author	PCR	Blood (PBMC)	3.10%	0.02
Wikgren et al. (2012)	Adults, national probability sample of Swedish general population ($n = 129$)	Both	General	No	Association of depression status and hypocortisolemic state with TL	Perceived Stress Questionnaire (30-item)	Published article (Spearman correlation only)	PCR	Blood (leukocyte)	6.00%	−0.26

TL assay CV = inter-assay coefficient of variation of T/S ratio.

[a] Sample sizes and demographics represent only those subjects with data for both PS and TL. For example, some studies enrolled from additional demographics but collected PS and TL on only a subset of subjects, while others collected PS and TL for a superset of subjects analyzed in the parent article.

[b] Data from NIEHS sister studies 1 and 2 represent two separate samples (Parks et al., 2011; Kim et al., 2011); further explanation is provided in Section 3.

within the Sister Study, which were treated as separate studies ("Sister Study 1" [Parks et al., 2011] and "Sister Study 2" [Kim et al., 2011]) in analysis.

We thus identified 23 eligible studies (Table 1). We were able to obtain both of the 2 primary endpoints (age-adjusted or raw PS–TL correlation) for 21 of these, and 1 of the primary endpoints for 1 other study. We could obtain neither endpoint of interest, nor a mathematical equivalent, for 1 study (Wikgren et al., 2012), which enrolled 129 subjects and reported a significant negative Spearman age-adjusted correlation between PS and TL ($r = -0.26$, $p = 0.0003$). Thus, we were able to obtain and meta-analyze at least 1 of the 2 primary summary measures for 22 studies, comprising a total of 8948 subjects.

3.2. Study characteristics

Eligible studies enrolled subjects representing a variety of demographics, including special populations such as subjects with past or current psychological stressors (e.g., caregiving duties for an ill relative, childhood or adulthood abuse, or intrauterine stress exposure), subjects with physical health conditions (e.g., knee osteoarthritis, fibromyalgia, or mastocytosis), and subjects with mood disorders (e.g., anxiety or depression). 10 of the studies (45%) enrolled subjects of both sexes, 11 (50%) enrolled only females, and 1 (5%) enrolled only males (Table 1). Study quality was variable; most did not report a priori analysis plans and sample size calculations or occurrence of missing data (Table A.1). Studies measured telomeres in leukocyte cells (11 studies), peripheral blood mononuclear cells (10 studies), lymphocytes (1 study), and salivary cells including an unspecified combination of cell types (1 study). (To justify pooling across cell types in analysis, we conducted a sensitivity analysis in which we meta-regressed the age-adjusted correlation on cell type [leukocytes vs. PBMC]; this analysis suggested no moderation by cell type.)

All eligible studies measured PS and TL cross-sectionally, although some studies measured additional variables retrospectively or prospectively or involved randomization to an intervention. All but 3 of the studies (Surtees et al., 2011; Wikgren et al., 2012; Carlson et al., 2015) measured PS using a full or abridged version of the validated Perceived Stress Scale (Methods A.1), in which respondents consider their experiences and feelings over the past month (Cohen et al., 1983). 2 studies used other validated measures: the Calgary SOSI index (Carlson et al., 2015) or the Perceived Stress Questionnaire (Wikgren et al., 2012). Another (Surtees et al., 2011) used a single 5-point item: "All things considered, how stressful do you believe that your life has been over the past ten years?" All studies measured TL using polymerase chain reaction (PCR) methods (Cawthon, 2002).

3.3. Unadjusted correlation between PS and TL

The unadjusted correlation was available for 22 studies and a total of 8948 subjects (Fig. 2A). 3 studies included in quantitative analysis reported significant negative correlations (Epel et al., 2004; Bersani et al., 2016; Georgin-Lavialle et al., 2014), as well as 1 included in qualitative description (Wikgren et al., 2012). The rest had nonsignificant point estimates. Visual assessments of available raw data supported modeling the PS–TL relationship as linear. Effect estimates showed significant heterogeneity ($Q = 43.0$; $df = 21$; $p = 0.003$; $T = 0.05$), suggesting that the true effect may have differed across studies due to, for example, inherent differences in the population sampled. The pooled correlation estimate did not indicate a significant linear relationship between PS and TL ($r = -0.05$; 95% CI: -0.11, 0.01; $p = 0.07$; $\alpha = 0.025$).

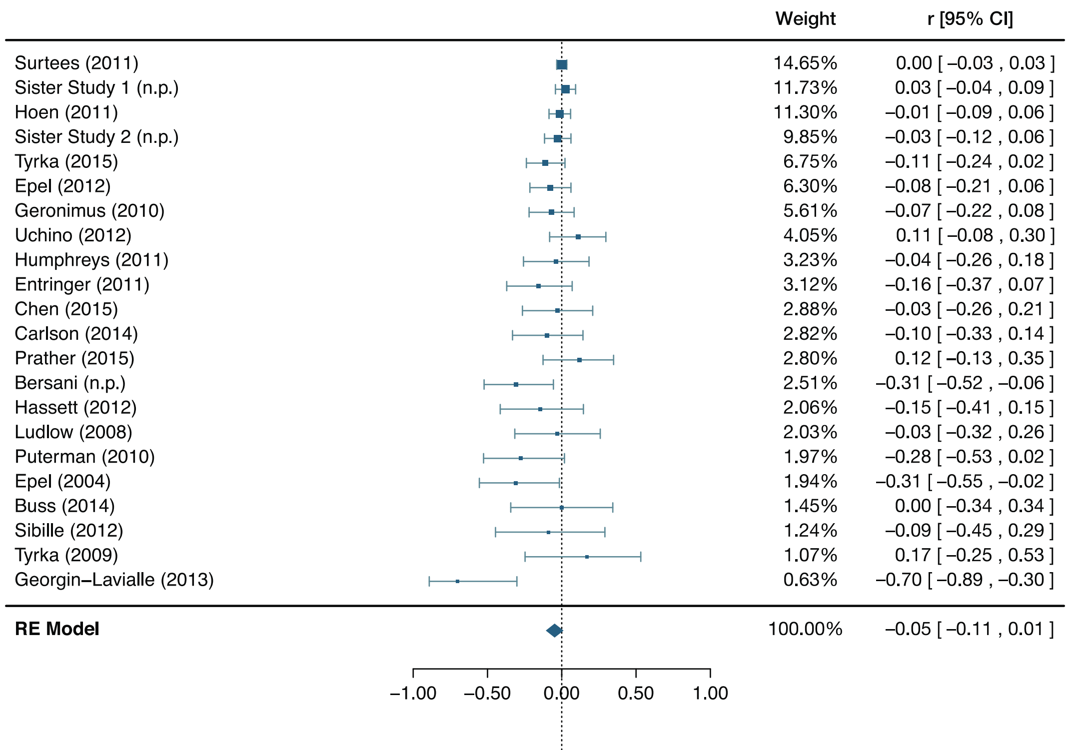

Fig. 2. Forest plots of unadjusted and age-adjusted correlations between perceived stress and telomere length. n.p. = not published. (A) Displays the unadjusted correlation. (B) Displays the age-adjusted correlation. Studies are displayed in descending order of weight (inverse variance). The pooled confidence interval is corrected for multiplicity between the 2 a priori endpoints.

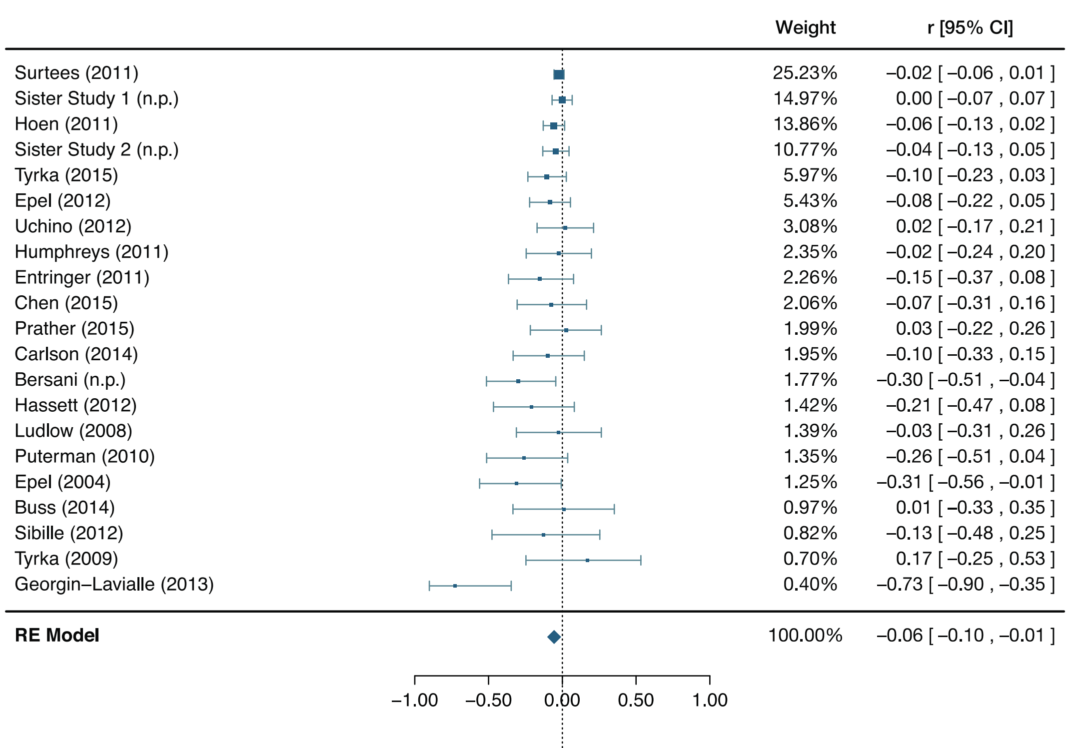

Fig. 2 (*continued*)

3.4. Age-adjusted correlation between PS and TL

The age-adjusted correlation was available for 21 studies and a total of 8724 subjects (Fig. 2B). The same 3 studies reporting a statistically significant unadjusted correlation also reported significant age-adjusted correlations (Epel et al., 2004; Bersani et al., 2016; Georgin-Lavialle et al., 2014), while the rest were null. Unadjusted and age-adjusted point estimates were similar in all studies

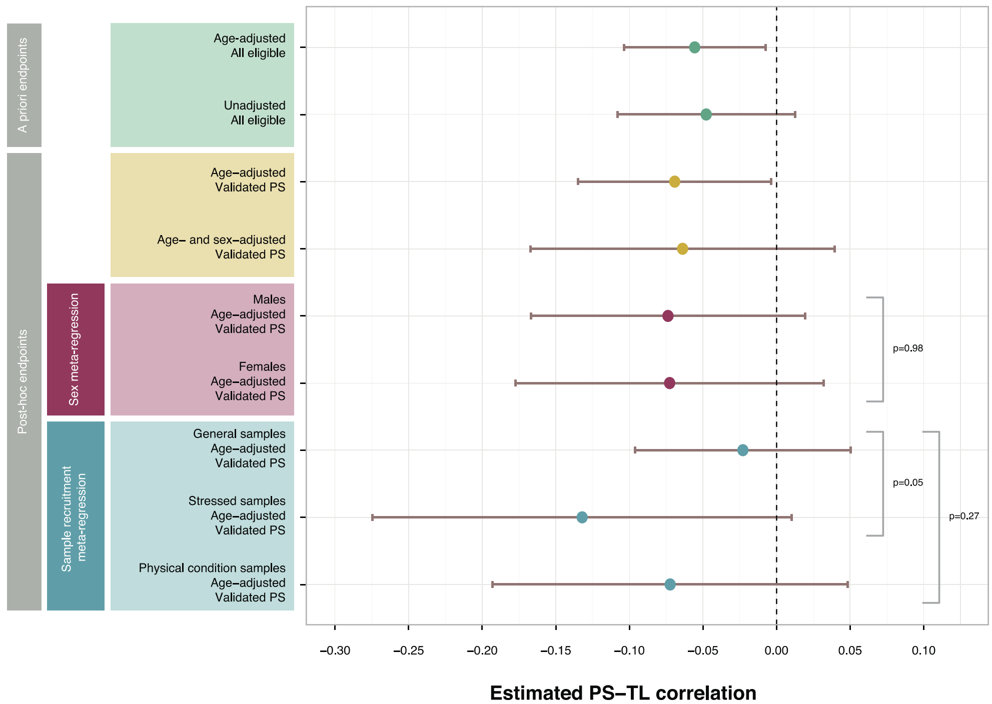

Fig. 3. Pooled point estimates from a priori, subset, and moderation analyses. For consistency, estimates from meta-regressive models are presented as fitted values rather than coefficients and represent the estimated PS–TL correlation for the relevant group. Thus, plotted confidence intervals correspond to testing for a nonzero correlation within the group of interest rather than a comparison of effect sizes across groups. Bracketed *p*-values correspond to meta-regressive tests of differences across groups.

for which both were available. As in the unadjusted analysis, there was evidence of between-study heterogeneity ($Q = 35.1$; df = 20; $p = 0.02$; $T = 0.03$). Adjusting for age, higher PS was associated with reduced TL ($r = -0.06$; 95% CI: −0.10, −0.008; $p = 0.01$; $\alpha = 0.025$), with a similar effect size to the unadjusted estimate.

3.5. Moderator and subgroup analyses

Results of post hoc analyses are displayed in Fig. 3. 1 study (Surtees et al., 2011) used an unvalidated measure of PS and was not included in the post hoc analyses. Removing this study did not substantively affect the age-adjusted point estimate ($n = 4371$ total, $r = -0.07$; 95% CI: −0.13, −0.004; $p = 0.01$; $\alpha = 0.013$). All subsequent post hoc analyses included only studies using validated PS measures.

To assess potential confounding by sex, we meta-analyzed the age- and sex-adjusted point estimates among the 10 studies enrolling both sexes ($n = 1787$ total), again yielding a similar, though nonsignificant, point estimate to primary analyses ($r = -0.06$; 95% CI: −0.17, 0.04; $p = 0.09$; $\alpha = 0.013$). A sensitivity analysis including both unvalidated and validated PS measures (as in primary analyses) would yield exactly the same result for this outcome because the single study using an unvalidated measure enrolled only females and therefore would not have contributed a sex-adjusted estimate.

We meta-regressively assessed possible moderation by sex, finding that the PS–TL relationship was similar between sexes (male: $r = -0.07$; 95% CI: −0.17, 0.02; female: $r = -0.07$, 95% CI: −0.18, 0.03; female vs. male: $b = 0.001$; $p = 0.98$; $\alpha = 0.013$). The latter coefficient represents the estimated difference in PS–TL correlation between female subsamples and male subsamples. Consistent with the lack of moderation by sex, Higgins' residual I^2 (the estimated proportion of "unexplained" variance that is attributable to true effect heterogeneity) was similar in the null model not containing sex (28.8%) and in the model containing sex (28.5%). A sensitivity analysis in which we included both unvalidated and validated PS measures yielded similar results (male: $r = -0.07$; 95% CI: −0.17, 0.02; female: $r = -0.06$, 95% CI: −0.16, 0.05; female vs. male: $b = 0.01$; $p = 0.75$; $\alpha = 0.013$).

Finally, meta-regressing on sample type suggested that the PS–TL relationship was comparable across samples recruited from the general population ($r = -0.02$; 95% CI: −0.10, 0.05) and in those recruited for a physical condition ($r = -0.07$; 95% CI: −0.19, 0.05; vs. general: $b = -0.05$; $p = 0.27$; $\alpha = 0.013$). The correlation was marginally, but nonsignificantly, stronger in stressor-exposed samples ($r = -0.13$; 95% CI: −0.27, 0.01; vs. general: $b = -0.11$; $p = 0.05$; $\alpha = 0.013$). Reported correlations and CIs represent the fitted estimates, while coefficients and *p*-values represent the estimated difference from general samples. Higgins' residual I^2 was reduced from 47.7% in the null model (not containing sex)[3] to 32.9% in the model containing sex. A sensitivity analysis in which we included both unvalidated and validated PS measures again yielded comparable results (general population: $r = -0.02$; 95% CI: −0.06, 0.02; physical condition samples: $r = -0.13$; 95% CI: −0.17, 0.03; vs. general: $b = -0.05$; $p = 0.19$; $\alpha = 0.013$; stress samples: $r = -0.13$; 95% CI: −0.25, −0.01; vs. general: $b = -0.11$; $p = 0.03$; $\alpha = 0.013$).

3.6. Publication bias

The funnel plot (Fig. A.2) and traditional Egger's test indicated significantly larger point estimates among smaller studies with larger SEs ($b = -1.03$; 95% CI; −1.78, −0.28; $p = 0.01$). However, as expected, sample size was strongly associated with sample type, with general samples tending to be much larger (median $n = 258$) than samples recruited for a physical condition (median $n = 61$)

[3] The null models used as comparators for the meta-regressive model containing sex and that containing sample type were not identical. The sex meta-regression model contained multiple observations for some studies and a corresponding random intercept by study; thus its null model contained these as well.

or psychological stressor (median $n = 83$). Removing study SE from a modified Egger's model did not significantly worsen model fit with the inclusion of fixed effects of sample type (LR = 2.60; $p = 0.11$), suggesting that the association of SE with effect size may be partly related to systematic differences in sample demographics between small and large studies. Using the Duval trim-and-fill method to correct for publication bias attenuated the correlation to nonsignificance ($r = -0.03$; 95% CI; -0.06, 0.005; $p = 0.09$; $\alpha = 0.025$). This suggests that the primary finding may be partly attributable to publication bias or other sample-size effects.

3.7. Comparative analysis for limitations of PS measures

We intended to conduct a comparative analysis of perceived, self-reported PS measures versus physiological measures. However, we found very few relevant studies (Epel et al., 2006; Tomiyama et al., 2012; Parks et al., 2009; Savolainen et al., 2015), and these reported inconsistent relationships between physiological measures of stress and TL, making our planned analysis unfeasible.

4. Discussion

Given burgeoning scientific interest in relationships between fundamental cellular physiology and psychology, we conducted a systematic review and meta-analysis using both published and unpublished data to examine the relationship between perceived stress and telomere length. We find a very small, significant, negative age-adjusted correlation that was not significant prior to adjustment for age. The relationship may be marginally, but non-significantly, stronger in samples with a known major stressor. Post hoc analyses suggest that results are similar when limited to studies using an empirically validated stress measure, between sexes, and between general population samples and those recruited for a medical condition.

A previous meta-analysis on this topic found a stronger negative correlation between perceived stress and telomere length (Schutte and Malouff, 2014). As discussed previously, this preliminary analysis had several methodological limitations; our more exhaustive search strategy allowed us to include more than 7,000 additional eligible subjects and resolved the double-counting and statistical issues of the previous analysis. The present, more comprehensive analysis resulted in a smaller pooled effect size than that reported previously.

Our results should be interpreted in light of several statistical and methodological limitations. We found statistically significant heterogeneity in effect estimates across studies, possibly arising from differences in sample demographics. Pooled statistical estimates must therefore be interpreted cautiously, as they average over the entire population from which all the studies are drawn and therefore may not appropriately represent the potentially unique "true effect" within any single study population. Additionally, we characterized the relationship between perceived stress and telomere length using the Pearson correlation because of its widespread availability and because limited raw data suggested its assumptions were generally fulfilled. Using directly comparable effect measures across studies is important for valid quantitative pooling and minimizes subjective influences that could occur with post hoc definition of categories or elimination of apparent outliers. However, this approach means that Pearson assumptions may occasionally have been violated in individual studies. We noted substantial inter-assay coefficients of variation in telomere length measures.

Our results are consistent with publication bias (the "file-drawer effect") (Borenstein and Hedges, 2009). To address this, we performed sensitivity analyses correcting for the effect of publication bias, which attenuated the observed age-adjusted relationship. There may be other mechanisms, not reflective of true publication bias, by which sample variability can be associated with effect size. For example, it is possible that smaller studies were less affected by statistical confounding or suppression, as they were more likely to recruit samples homogeneous on confounders such as health conditions (D'Mello et al., 2015; Zhao et al., 2013). The "p-curve" (Simonsohn et al., 2014), a more precise test of publication bias that does not rely on sample standard error, was not feasible in this case due to the small number of positive findings.

Although we were able to assess moderation effects of several demographic and methodologic factors, other variables known to be associated with telomere length, such as lifestyle factors (Puterman et al., 2010; Prather et al., 2014), health conditions (D'Mello et al., 2015; Zhao et al., 2013), medications (Saliques et al., 2011), and clinical depression (Cai et al., 2015), were reported too infrequently in the literature for meta-analysis. Indeed, individual studies included in our analysis suggested moderation by factors such as smoking (Chen et al., 2015) and physical activity (Puterman et al., 2010). We used partial correlations to adjust for age as a known confounder of the PS–TL relationship, but were not able to assess its effect as a possible moderator due to limited availability of individual participant data. Moderation by age could occur if stress effects are cumulative over the lifespan, causing a stronger relationship between perceived stress and telomere length among older versus younger subjects. Alternatively, many age-related diseases are associated with a heightened cortisol response to challenge; thus, older subjects may be more physiologically susceptible to a given stressor than are younger subjects (Otte et al., 2005). Indeed, a study included in this meta-analysis found a relationship between perceived stress and telomere length only among subjects aged at least 55 years (Parks et al., 2009).

Another theoretically challenging extraneous variable is clinical depression. While perceived stress and depression are strongly associated, depression is a more severe state characterized by substantial neurobiological alterations. A past review found clinical diagnosis of depression, but not self-reported depression, to be associated with telomere length, suggesting the possibility of a threshold effect rather than a continuous response (Lindqvist et al., 2015). Additionally, past research has suggested that a history of major depression mediates the relationship between perceived stress and telomere length (Cai et al., 2015); simple covariate adjustment for depression status aimed at reducing confounding may therefore aggravate rather than alleviate bias due to depression (Hernán et al., 2002). We recommend that future work use more sophisticated statistical modeling approaches to address bias due to depression (e.g. Valeri and Vanderweele, 2013).

The very small magnitude of our finding may reflect limitations of perceived stress measures. One of the largest studies of telomere length (Cai et al., 2015) found that stressful event exposure alone (not accounting for perceived stress) predicts telomere length. Additionally, short-term stress may impact telomere biology only briefly (Cai et al., 2015), and longitudinal measures of perceived stress may better capture chronic effects (Monroe and Simons, 1991); elevated perceived stress over a lifetime may play an important role not fully reflected in current telomere literature. In addition to chronic stress effects, severe life stressors and events across the life course (including early life) appear to have long-lasting associations with health effects, including telomere length (Shonkoff and Garner, 2012; Blaze et al., 2015; Price et al., 2013; Cohen et al., 2013). Thus, perceived stress over the past month may be limited as a single measure. Ideally, future research should increasingly adopt longitudinal designs rather than the current cross-sectional designs. By measuring multiple stress constructs – perceived stress, physiological stress, and stressful life events – as well as telomere length repeatedly within each subject, such designs would clarify the temporal ordering of the integrated stress response, changes in telomere length, and changes in aforementioned extraneous variables (Fig. 1).

In our secondary analysis of moderation by sample type, we did not exclude control subjects from studies recruiting stressor-exposed samples or samples with physical conditions. An alternative approach of including only samples with homogeneous stressor exposure would severely limit power and could produce artificial range restriction (Hunter et al., 2006). The ideal approach, namely using subject-level data to classify subjects by stressor exposure, was not possible given limitations in data availability. A caveat of our classification approach is potentially increased heterogeneity among "stressor-exposed" samples due to the inclusion of control subjects. Additionally, limited availability of raw data precluded assessment of the subject-level relationship between stressor exposure and PS.

In context of these limitations, our findings indicate that 2 subjects differing on perceived stress by a full standard deviation differ on average by 6% of a standard deviation on telomere length. Equivalently, variations in perceived stress appeared to account for less than 1% of variability in telomere length. Our finding of an effect size of $r = -.06$ is similar to the effect size of obesity on TL ($r = -.057$) (Muezzinler et al., 2014), approximately 18–35% that of blood pressure on TL ($r = -0.34$ and $r = -0.17$ for males and females, respectively) (Benetos et al., 2001), approximately 30% that of incident coronary heart disease on TL (OR = 1.44 for highest-versus lowest-tertile TL[4]) (Brouilette et al., 2007), and approximately 30% that of depression on TL ($r = -0.205$) (Ridout et al., 2016). As noted previously, this very small effect size may, in theory, belie aggregate effects of practical impact. If reflective of a true causal relationship between short-term stress and telomere biology, the observed effect could potentially translate over the lifespan into cumulatively divergent cellular health among individuals with different levels of chronic stress. Such a divergence could culminate in clinically relevant differences in telomere biology by old age.

In completing what we believe to be the most comprehensive meta-analysis on this topic to date, we find a very small age-adjusted decrease in telomere length with increases in perceived stress that appears to be approximately equivalent to that seen in the relationship between obesity and telomere length. Emerging research on this topic, such a large new study finding an effect size similar to our pooled estimate (Lynch et al., 2016), will help verify our findings as well as improve statistical power to more precisely assess confounders and moderators. Our finding is qualified by likely publication bias, although fully parsing the effects of true publication bias from other sample-size correlates is challenging. Overall, our analysis indicates that the literature does not currently support a strong role of perceived stress (as measured over the past month) in shortening telomeres, though the relationship may be stronger among individuals facing adversity.

In light of the high incidence of reported stress as well as the complex interplay between life events, perceptions of their importance, and development of disease, our findings highlight the need for additional longitudinal research. Development of multidimensional lifespan models of reported, perceived, and physiological stress, use of standardized telomere assays, and incorporation of known extraneous variables (such as medications, health conditions, lifestyle factors, and clinical depression) would strengthen such future work.

[4] This OR is equivalent to Cohen's d effect size (which is comparable to the Pearson correlation) (Sánchez-Meca et al., 2003), of $\log(1.44) * \frac{\sqrt{3}}{\pi} = 0.20$.

Author contributions

M.M. and N.K. conceived the study. M.M., N.K., E.E., and M.D. contributed to the analysis plan. M.M., S.K., and D.S. collected data. M.M. performed statistical analyses. M.M., N.K., E.E., M.D., C.P., and D.S. wrote the manuscript.

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Research transparency

Analysis code and other study materials are publicly available at https://osf.io/e9tg8/.

Competing interests

The authors declare that they have no competing financial interests.

Ethics

This research was reviewed and granted a waiver by the appropriate ethics committee (Stanford University IRB).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbi.2016.02.002.

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